AUTISM | CELLULAR TRANSPORT | A MOTHER'S TOUCH

ResearchNews

ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

SPRING 2008

Off to a good start

AHFMR teams lead the way in studies of maternal nutrition and preterm birth

On the cover

Originally from Quebec, **Valéry Goulet** received her graphic design training from Université Laval and has been working in the world of design for the past 7 years. In addition to working as art director at a graphic design studio in Edmonton, her passion for design also led her to found her own illustration company: ValéryDesignwrks.

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AHFMR MISSION

AHFMR supports a community of researchers who generate knowledge, the application of which improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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We have extended the deadline for our readership survey

We want to hear from you!
Please help us in our efforts to continually improve by telling us what you like and what you don't like about the redesigned *Research News*.

What's in it for you?
Complete our readership survey by July 31, 2008 and your name will be entered to win ***a prize valued at $250***. To access the survey go to **www.ahfmr.ab.ca/readershipsurvey/** or call, write, or e-mail us at the address opposite and we would be happy to send you a print version of the survey.

It is only with your help that we can get the information we need to improve the quality of this magazine for all of our readers.

Thank you!

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Where art and science meet

Celebrated physicist and novelist Dr. Alan Lightman discusses the overlap between the arts and sciences.

Dr. Alan Lightman is one of a relatively small band of people who achieve excellence in both the sciences and the humanities in their working lives. Even as a young boy growing up in Memphis, Tennessee, his passions were divided equally between these two worlds. "As a child, I wrote a lot of poems. I was mesmerized by the sound and movement of words. As if by magic, words could create scenes and emotions. I also did scientific experiments in a cramped lab in a large bedroom closet. I collected equipment: test tubes, Petri dishes, flasks, batteries, photocells, resistors. I delighted in this equipment."

One of his fondest memories is of a rocket project he attempted at the age of 14. He built the rocket, developed his own rocket fuel, and crafted the ignition source from the flashbulb of a Brownie camera. From his thrust calcula-

> "I had sacrificed reality for aesthetics"

tions, he expected the rocket to fly half a mile or so. On launch day, his audience consisted of his "constantly awed" younger brothers and an assortment of neighbourhood boys.

The launch went well; but after rising only a few hundred feet, the rocket crashed to earth. The tail fins had come off. "It was then, with a sudden clarity, that I realized that instead of riveting the tail fins, I had just glued them on because I decided the rivets were too ugly. I had sacrificed reality for aesthetics."

The episode of the rocket project was the first time Dr. Lightman's scientific and artistic inclinations collided, but far from the last. The constant tension between art and science in his own life is a source of his witty and insightful observations.

"Roughly speaking, the scientist tries to name things while the artist tries to avoid naming things. To name a thing, you must distill it, attempt to identify it with some kind of clarity and precision. Consider the word *electron*, a type of subatomic particle. As far as we know, all the zillions of electrons in the universe are identical. To a modern physicist, the word *electron* means a particular equation which summarizes everything we know about electrons.

"The objects and concepts the novelist deals with cannot be named. I might use a word like *love*, but it doesn't convey much to the reader. For one thing, there are a thousand different kinds of love. The novelist must also communicate the particular sensation of love. All this must be shown to the reader—not named, but shown through the actions of the characters. And if love is shown, then each reader will experience it in their own individual way. Love means one thing to one person, and a different thing to another.

"All electrons are identical, but every love is different. The novelist doesn't want to eliminate these differences—to try to clarify the meaning of love until there is only a single meaning. No such distillation would represent love."

> "Both the novelist and scientist are seeking truth"

Although the differences between scientists and artists are often striking, Dr. Lightman notes that there is also substantial common ground between the two. One area is the concept of truth. "The folklore is that novelists make up most of what they write about, and scientists make up nothing. Both views are false. Creative imagination and inventiveness have always been hallmarks of good scientists and good novelists."

And just as the scientist must agree with the body of known facts, so must the novelist. "The straitjacket of the novelist is the large catalogue of known behaviour and psychology of *Homo sapiens*—a catalogue we call human nature. These are the facts of emotional truth by which the novelist must live.

"Both the novelist and scientist are seeking truth. For the novelist, truth is in the mind and the heart. For the scientist, truth is in the world of mass and force."

Dr. Lightman argues that both ways of knowing are important. "I've come to learn that we need questions with answers and questions without answers. Both kinds of questions are part of being human." ❋

About the researcher
Dr. Alan Lightman is adjunct professor of humanities at the Massachusetts Institute of Technology. His novels include *The Diagnosis*, *Einstein's Dreams*, and *Ghost*. He was the keynote speaker at the Art and Science Symposium held in Edmonton in November 2007 as part of the Edmonton Cultural Capital 2007 program.

Autism

An AHFMR researcher is looking for ways to diagnose autism earlier.

One out of every 150 children in Canada has autism spectrum disorder. Yet, because of the shortcomings of current diagnostic methods, autistic children usually aren't identified until the age of four or five. Consequently, their access to any type of systematic treatment is delayed.

In the hope that children will benefit from earlier diagnosis, AHFMR Scholar Dr. Lonnie Zwaigenbaum embarked several years ago on an ambitious study—looking for early behavioural signs of autism in infants.

Autism is a disorder involving the development of the nervous system. Some of the best-known symptoms are delays in language development; difficulties in understanding and participating in social relationships; and preoccupations with repetitive tasks or behaviours. Autism is thought to develop in the womb; however, Dr. Zwaigenbaum notes that children with the disorder often seem typical in their first few months. "But then the more obvious difficulties in social engagement and communication skills may emerge in the latter half of the first year of life."

In an attempt to identify effective predictors of an autism diagnosis, Dr. Zwaigenbaum and his colleagues chose to study the younger siblings of children already confirmed as autistic. The siblings' own risk of developing the disorder was considered to be about 9%, significantly higher than that for the general population.

Infants in this high-risk group were assessed on a variety of behavioural measures, such as their ability to track visual stimuli, their response to communication, and their overall temperament. They were tracked from the age of six months to the age of three years, at which point they were independently evaluated for autism. The early results of this study showed that, by the time they were a year old, children who would later be identified as autistic could be distinguished from those who would not receive such a diagnosis. Quite a significant finding.

> Dr. Lonnie Zwaigenbaum looks for early behavioural signs of autism in infants

Since his arrival in Edmonton in 2006, Dr. Zwaigenbaum has focused on two key projects made possible by AHFMR funding. The sibling project—is set to continue, but with some new components. Dr. Zwaigenbaum hopes to begin brain-imaging work on this high-risk infant group to compare early behavioural signs of autism with changes in brain development.

For his second major research project, Dr. Zwaigenbaum will look at pre-school children already assessed as autistic. He hopes to identify the types of treatment that will put these kids in the best possible position to make the transition to school. The provinces of Nova Scotia, Quebec, Ontario, and British Columbia are involved in this study. Since each province provides a different level of funding for treatment of children with autism, Dr. Zwaigenbaum thinks it will be possible to compare the different treatment models to see whether they lead to differences in progress and outcomes.

Autism

He is also working with a group of colleagues to study environmental factors that might play a role in the development of autism. He wants to know how these factors interact with genetic susceptibility. Early research with twins showed that, if a child has autism, an identical twin is more likely to develop the disorder than is a fraternal twin. In other words, genetics plays a role—but it probably doesn't tell the whole story.

Dr. Zwaigenbaum's passion for autism research emerged during his early training. His respect for autistic children and their families, and his understanding of the significant daily challenges they face, is readily apparent. He is also seeking insights into the nature of this disorder, about which so much remains unknown.

"There's certainly a lot we still need to learn. It's the interesting clinical questions, as well as a personal interest in helping kids with autism and their families, and the enjoyment of working with them, that brought me to this field." ■

About the researcher
Dr. Lonnie Zwaigenbaum is an *AHFMR Scholar* and an associate professor in the Department of Pediatrics at the University of Alberta Faculty of Medicine and Dentistry.

Selected publication

Zwaigenbaum L, Thurm A, Stone W, Baranek G, Bryson S, Iverson J, Kau A, Klin A, Lord C, Landa R, Rogers S, Sigman M. Studying the emergence of autism spectrum disorders in high-risk infants: methodological and practical issues. *Autism and Developmental Disorders*. 2007 Mar;37(3): 466-480.

Recommended websites

Autism Society Canada
http://www.autismsocietycanada.ca/

Autism Canada Foundation
http://www.autismcanada.org/

Is there a link between vaccinations and autism?

Autism expert Dr. Lonnie Zwaigenbaum addresses the persistent rumours.

IF YOU ARE THE PARENT OF A YOUNG CHILD, you may have had second thoughts when taking your toddler in to the doctor for a routine vaccination. You may have been wondering about the rumours that have been circulating for a number of years that this vaccine could cause autism in your child. But the evidence is in: There is no link, and the rumours should be laid to rest.

■ Autistic children don't start to show atypical behaviour until they are 12 to 18 months of age—right around the time that many children receive their childhood vaccinations.

AHFMR Scholar Dr. Lonnie Zwaigenbaum (see story on preceding page), who holds an endowed chair in autism research through the Stollery

The evidence is in: There is no link

Foundation, explains the confusion. "The concern is there because I think that there truly are families who notice the initial signs of autism shortly after vaccination. However, studies have clearly shown that rates of autism are similar in vaccinated and non-vaccinated children; and that, among children with autism in these two groups, the timing and the pattern of onset is very similar."

In 1998 a study by British gastroenterologist Dr. Andrew Wakefield and a group of colleagues heightened concern around this issue by claiming that there was a link between the MMR (mumps, measles, rubella) vaccine and autism. Because the study was published in a prestigious medical journal, and because it generated significant public debate, the claims have remained credible in the minds of the public.

Years of subsequent research have failed to uphold Wakefield's conclusion. In fact, in 2004—six years after publication—10 of the 12 people who contributed to the original study retracted its claims on the basis of insufficient data. Dr. Zwaigenbaum understands, however, why the rumours still persist.

"What's compelling to a scientist, in terms of large sample sizes, may be less compelling to a family. A family wants to know more at an individual level: Is there a possibility that the vaccine might increase risk? Personal stories can be more powerful than large population-based research studies," he explains.

But how do these large population-based studies work? To test if a link exists between a certain vaccination and autism, one need only find out whether there is a higher rate of autism in the segment of the population that received the vaccination than there is in the segment of the population that did not. Dr. Zwaigenbaum describes a *New England Journal of Medicine* article that compared

Genetic influences play a strong role in the development of autism

400,000 children who were vaccinated with 100,000 who were not. The groups showed equal rates of autism. So something else must be underlying the development of the disorder.

Other concerns centre around the use of a vaccine preservative called thimerosal and the incidence of autism. Information gathered by the Department of Public Health in California refutes this connection. Statistics covering the period from 1995 to 2007 show that rates of autism continued to increase even after thimerosal was phased out of vaccines in 2001.

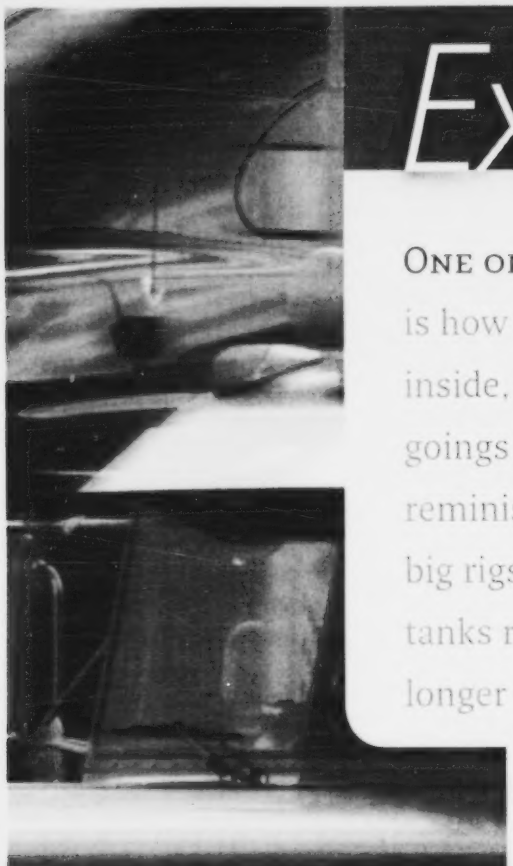
If vaccines can be discounted as a cause of autism, what factors are relevant? Dr. Zwaigenbaum points out that genetic influences play a strong role in the development of autism, although no single "autism gene" has been identified to date. "There's emerging evidence that specific genes that are involved in the risk of autism seem to play a role in brain development," he explains.

So how would Dr. Zwaigenbaum respond to parents wondering whether or not to vaccinate their child? "As a pediatrician, I'd certainly recommend vaccination, but I also respect that there's a lot of information out there that parents are processing. I think that our role is to help parents make informed decisions, but also encourage healthy practices such as vaccination."

About this feature

Exchanging pla

ONE OF THE MYSTERIES OF STRUCTURAL BIOLOGY is how things move from the outside of a cell to the inside, and then back out again. The comings and goings of molecules and ions into and out of cells are reminiscent of the action at a busy truck stop, where big rigs pull in to refuel, then leave once their gas tanks read "full." Should a truck linger at a pump for longer than expected, chaos can result.



Dr. Frank Visser studies the constant movement of certain substances in and out of our cells.

Cells also have a lot of action going on inside them, with many substances changing places from outside to inside and vice versa. But what makes a cell welcome these materials? And how does a cell remove the ones that have had their stay? These are questions that continue to puzzle scientists.

Dr. Frank Visser, an AHFMR-supported post-doctoral fellow at the University of Calgary, is one of those scientists. In the lab of AHFMR Scientist Dr. Jonathan Lytton, he has been helping unravel the mystery of how calcium moves into and out of cells. When you consider that ·ium triggers vital functions in the body—heartbeats, hormone secretion, and communication from brain cells—you have to acknowledge that it's important work.

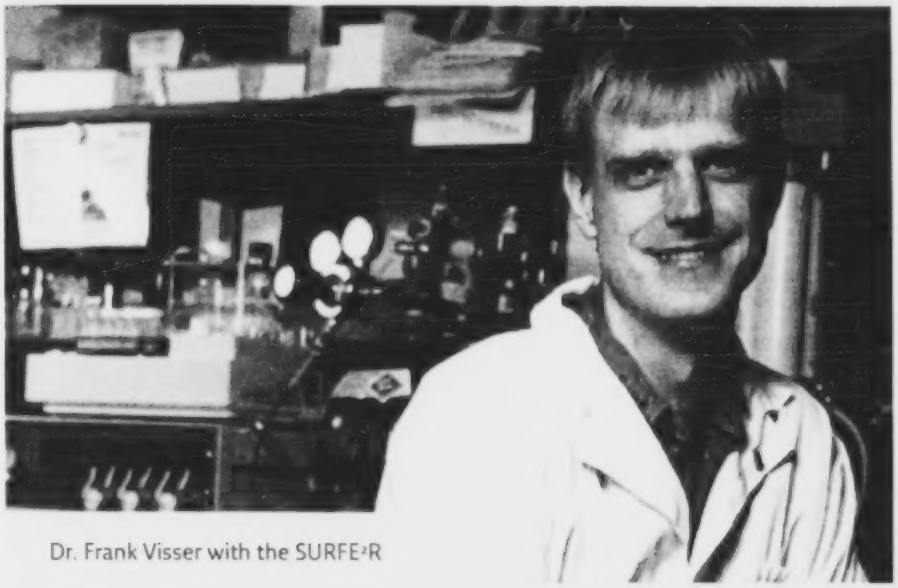
Much is already known about how cells move calcium and other nutrients in and out. For example, a certain family of proteins present in a cell membrane play critical roles in the transport of calcium. Called sodium/calcium (Na^+/Ca^{2+}) exchangers, these proteins keep the amount of calcium entering a cell in check. Once the maximum permitted quantity of calcium is inside a cell and has gone to work signalling a muscle contraction or some other important response, the exchange system must function properly to regulate the strength and duration of that response. When something goes wrong with the exchange system, a serious problem can arise—possibly heart failure or stroke.

Dr. Visser concentrates on the structural and functional properties of sodium/calcium exchange systems. In particular, he studies a type of exchanger that is important for vision, learning and memory, and skin pigmentation. We know that, in such exchanges, potassium ions as well as calcium ions are excreted from the cell. However, we don't know which ions leave first, or why.

Cool tools

To study the exchange process more closely, Dr. Visser uses SURFE²R technology—instrumentation that can detect even the slightest difference in electric charge on delicate isolated cell membranes, and measure that difference with a degree of accuracy not previously attainable. Because the charge moving across a cell membrane is so very weak, it is important to use equipment of the highest sensitivity in this research.

After 10 years in the academic research field, Dr. Visser has moved to the next stage of his career. He recently accepted a post as a research scientist with SemBioSys, a Calgary-based firm that produces proteins of pharmaceutical importance. ❋



Dr. Frank Visser with the SURFE²R

Surfing in science

It may not be quite as much fun as catching a wave, but using the German-made SURFE²R (Surface Electrogenic Event Reader) technology to measure tiny movements within the human body can be just as exhilarating and rewarding.

SURFE²R technology allows researchers to investigate *cell transporter proteins*, which control the movement of nutrients, signalling molecules, and ions into and out of a cell or between the internal compartments of a cell. This traffic flow is extremely important for a cell's proper functioning and, not surprisingly, plays a fundamental role in an organism's well-being. However, the proteins that aid in transport can be very difficult to isolate and measure.

With SURFE²R technology, researchers use prepared membranes isolated from cells to study transporters that are *electrogenic* in nature; that is, those which control the movement of electric charge. This technology is highly sensitive: it can detect even very weak electric currents.

Unlike the colourful surfboards you'll find on a beach, the SURFE²R instrument comes in an unassuming "bench-top beige"; essentially, it's a metal box with a few dials and buttons on it. At the heart of this equipment, however, lie small sensor chips with gold electrodes that detect changes in electric charge.

In the fall of 2007, SURFE²R technology arrived at the University of Calgary's Department of Biochemistry and Molecular Biology—its first appearance on North American soil. ❋

Dr. Visser's supervisor, AHFMR Scientist **Dr. Jonathan Lytton**, received an ***AHFMR Major Equipment Grant*** to purchase the SURFE²R technology.

About the researcher
Dr. Frank Visser was, until recently, an ***AHFMR Post-doctoral Fellow*** in the Department of Biochemistry and Molecular Biology at the University of Calgary.

Selected publication
Visser F, Valsecchi V, Annunziato L, Lytton J. Analysis of ion interactions with the K^+-dependent Na^+/Ca^+ exchangers NCKX2, NCKX3, and NCKX4: identification of Thr-551 as a key residue in defining the apparent K+ affinity of NCKX2. *Journal of Biological Chemistry* 2007 Feb 16;282(7):4453-4462.

Nature, nurture, and a mother's touch

Dr. Michael Meaney's research turns the old nature-versus-nurture debate on its head. His work shows that a mother's touch can trigger genes that shape her child's stress response.

NATURE VERSUS NURTURE. It's an age-old debate about the relative roles played by our inherited characteristics and our environment in determining who we become. The controversy over which factor is dominant has raged on for centuries: To what extent are we preprogrammed by our DNA, and to what extent are we shaped by our experiences and the world around us? Psychologist Donald Hebb called it a false question—akin to asking whether length or width contributes more to the area of a rectangle. Now an emerging field called epigenetics is providing new evidence that nature and nurture are, in fact, inextricably linked, and information on how they work together.

A mother's touch may help shape her child's stress response

Epigenetics is the study of changes in the activity of the gene that occur without any changes in the structure of its DNA. For example, factors such as maternal stress and nutrition and the infant's own diet (nurture) have been shown to change gene function without altering the DNA sequence (nature) in any way. Epigenetics can help explain how identical twins, who have exactly the same genes, may have different experiences of disease: one twin may develop cancer or schizophrenia while the other does not.

Dr. Michael Meaney (L) and Peter Lougheed (R)

Dr. Michael Meaney, the winner of AHFMR's inaugural Lougheed Prize, is a leading epigenetics researcher. He was one of the first researchers to identify the importance of a mother's care in the development of her child, as well as the child's ability to cope with stress later in life.

> "Parental care can have an even bigger impact than we ever dreamed"

It all started with Dr. Meaney's observations of female rats and their nurturing behaviour toward their offspring—in other words, how frequently these rat mothers lick their pups. He discovered that the level of care changes the chemistry of the DNA in certain genes involved in the pup's stress response. "The interaction causes these genes to become either more or less active," explains Dr. Meaney. "Genes can't function independently of their environment. So every aspect of our lives is a constant function of the 'dialogue' between environmental signals and the genome." This is epigenetics.

Dr. Meaney and his team found that frequent licking had immediate impact on the growth of the rat pups. It enhanced the activity of growth hormones and decreased the release of *glucocorticoids*—compounds involved in the stress response. "For us, the holy grail was to identify the path that was being altered by this licking behaviour," he says. "We identified the one small region on the gene that responds to maternal care and directs changes in the brain cells."

Since these observations in rats lead us to wonder—quite naturally—about similar effects in people, Dr. Meaney is now embarking on studies which will look at child development in humans. The weight of a child at birth is a remarkably reliable predictor of the health of that child throughout life; high birthweight predicts good health; low birthweight predicts poor health. Factors that contribute to low birthweight include high levels of maternal stress, poor maternal nutrition, and tobacco and alcohol consumption by the mother. But if the mother's glucocorticoid levels are high, they can contribute to low birthweight too. Yet, as he points out, many babies with a low birthweight do very well later in life. So postnatal care must be one of the factors that are capable of reversing these early effects.

"The bottom line seems to be that parental care can have an even bigger impact than we ever dreamed on our children's lives," says Dr. Meaney. "We're just starting to learn what that means." ❋

About the researcher

Dr. Michael Meaney is a professor in the Department of Psychiatry and the Department of Neurology and Neurosurgery at McGill University in Montreal, as well as the director of the McGill Program for the Study of Behavior, Genes and Environment. He is the first recipient of the ***AHFMR Lougheed Prize***, an award established to honour former premier Peter Lougheed for his key contributions to the creation of the Alberta Heritage Foundation for Medical Research (AHFMR).

Off to a good start

Two new AHFMR research teams are leading the way in studies of maternal nutrition and preterm birth.

WHETHER YOU'RE COMPETING IN A RACE or beginning a life, getting off to a good start counts. For babies, a good start means setting out on the right track for healthy development, both physical and mental. And beginnings aren't only about the babies themselves and their immediate environment in the womb. The physical and mental health of mothers also plays a crucial role.

■ These concepts are being explored by two of the teams that were successful in AHFMR's first-ever Interdisciplinary Team Grants competition. Although their perspectives are different, the teams share a common goal: getting babies off to a good start.

Maternal nutrition

THE OLD ADAGE "you are what you eat" still holds true. Good nutrition is essential for brain growth and development in particular, and for good physical and mental health in general. And yet poor nutrition is extremely common, even in Alberta. The impact of a poor diet is magnified in pregnancy—when a woman's nutritional needs increase and the fetus depletes maternal reserves.

■ "We know the level of nutrition a mother needs to meet her own basic requirements and those of her unborn infant through the course of a pregnancy," says the University of Alberta's Dr. Catherine Field. "But very little has been done to define nutrition in terms of functional outcomes; for example, how nutrition affects the mental health of the mother or the neurological development of the child. That's what our team is exploring."

Dr. Field is one of the leaders, with Dr. Bonnie Kaplan and Dr. Deborah Dewey, of the team officially called "The Impact of Maternal Nutrient Status During Pregnancy on Maternal Mental Health and Child Development". The team has paraphrased this for the sake of convenience, and refers to itself as the Alberta Pregnancy Outcomes and Nutrition (APRON) team.

Why look at the mental health of mothers? Because it matters. Maternal depression, for instance, is strongly associated with poor physical, emotional, and behavioural development in newborns. Depression can also influence the mother-child interaction, including how a mother feeds her baby. Children of depressed mothers have reduced muscle tone and lower activity levels, along with increased behavioural problems. They also score lower on developmental tests.

Why look at the neurological development of children? Because it matters too. Many neurodevelopmental disorders appear to be increasing. These include attention-deficit hyperactivity disorder (ADHD), learning disorders such as reading disabilities, and autism spectrum disorders. These disorders can significantly affect children's performance in school, as well as their physical and mental health and that of their families.

"We need to look at maternal nutrition and the brain development of children"

For the APRON team, the link is nutrition. "There's been an explosion of research around the world on nutrition and brain function," says APRON team co-leader Dr. Bonnie Kaplan from the University of Calgary. "And it's not just research—people are being treated successfully with various nutritional interventions. This needs to be explored further. We need to understand the relationship between nutritional inadequacy and depression in women before and after birth. We have an incredible opportunity to do this in Alberta."

The APRON team is composed of 16 researchers from the University of Calgary, the University

The impact of a poor diet is magnified in pregnancy

of Alberta, and the University of Tilburg in the Netherlands. The team includes such health professionals as dietitians, psychologists, and physicians, as well as young people who are training in these areas. "With direct links to the health professionals of today and tomorrow, we have the opportunity to translate new understanding about maternal nutrition into action that improves maternal and infant health," says Dr. Kaplan.

Insights into mood disorders in mothers and the health of their babies will come from a study involving 10,000 pregnant women in Calgary and Edmonton (5,000 from each city). The work involves complete assessments of maternal mood and maternal nutrition, as well as of the neurodevelopment of the child from infancy to age three. Nutrition will be evaluated from reports of what individuals eat, and also from measurements of the levels of various nutrients in their blood.

"The information we collect will be a rich database not only for our team but for future researchers," Dr. Field points out.

The team will ask questions in three main areas: women's mental health, birth, and child development.

"In [the area of] women's mental health, we've known for a long time that many women struggle with depression after birth," notes Dr. Kaplan. "The latest research shows that some women experience altered mood during pregnancy—and not just women with a history of depression. So we will be looking at maternal mood throughout pregnancy and after childbirth. There are hints in the literature that nutritional insufficiency contributes [negatively] to maternal mood. We hope that we'll be able to understand more about this connection."

The second area centres around birth and birth outcomes: labour, Apgar assessments of the health of newborns, their birthweight, any congenital anomalies, and their neurodevelopmental function. The team will also collect blood from the umbilical cord and a small swab from inside the mouth of each infant for future genetic analysis.

The third area is the neurological and cognitive development of children. Is there a relationship between nutrients taken in by the mother during pregnancy and the development of disorders such as ADHD, autism, or learning disabilities in the child? In this part of the team's work, led by the University of Calgary's Dr. Deborah Dewey, mothers will periodically report on their children's physical and mental development. Members of the team will do a complete assessment of mental ability and motor skills of a random subset of children when those children are three years old. A key goal is to find predictors of neurological development in the child from the nutrient intake of the mother.

"Some women experience altered mood during pregnancy"

For example, we already know that folic acid, a B vitamin, reduces the risk of certain serious

birth defects called *neural tube defects*, which affect the brain and spinal cord. One of these, spina bifida, is the second most common birth defect in Canada. In this disorder, an abnormality of the spinal column results in varying types and degrees of handicap, including bending of the spine, paralysis, learning disabilities, and mental retardation.

Because of the importance of folic acid in preventing neural tube defects, flour, pasta, and cornmeal products are fortified with the nutrient. When fortification programs began in the late 1990s, food manufacturers added a lot more folic acid than required because little was known about its shelf life. But now that they have had more experience with fortification, manufacturers have reduced the amount of folic acid added to food.

"Some researchers are concerned that we're going to see a resurgence in neural tube defects," says Dr. Field. "There is a simple solution—just add more. But we don't know what impact this will have on mothers and infants, as too much folic acid may increase the risk of cancer. We really need to know whether the current recommendation is appropriate.

"This is the kind of issue that our team will be able to get a handle on. And there's much more to find out. We've known for years about straightforward relationships like vitamin C and scurvy. But when we're into complex brain development and neural function, it's unlikely that only a single factor is involved. We will be measuring the intake of vitamins, minerals, and omega-3 fatty acids, and whether those levels are sufficient. The potential to improve health is amazing. We're eager to get going."

Dr. Bonnie Kaplan

Dr. Catherine Field

Dr. Deborah Dewey

About the team leaders

Dr. Bonnie Kaplan is a professor in the departments of Paediatrics and Community Health Sciences in the Faculty of Medicine at the University of Calgary.

Dr. Catherine Field is a professor of nutrition and metabolism in the Department of Agricultural, Food, and Nutritional Science at the University of Alberta.

Dr. Deborah Dewey is a professor in the departments of Paediatrics and Community Health Sciences in the Faculty of Medicine at the University of Calgary.

Selected publications

Kaplan BJ, Crawford SG, Field CJ, Simpson JSA. Vitamins, minerals, and mood. *Psychological Bulletin*. 2007 Sep;133(5):747-760.

Field CJ, Van Aerde JE, Robinson LE, Clandinin MT. Effect of providing a formula supplemented with long-chain polyunsaturated fatty acids on immunity in full-term neonates. *British Journal of Nutrition*. 2008 Jan;99(01):91-99.

Alberta has the highest rate of preterm birth in the country

Preterm birth

PRETERM BIRTH is an important health concern in this country, as it is in industrialized nations around the world. In Canada, preterm birth (before 37 completed weeks of pregnancy) accounts for about 80% of all infant mortality in the period just before or after birth.

■ There's even more concern in Alberta, which has the highest rate of preterm birth in the country: more than 9% of live births. While many of these babies do well, preterm birth is associated with developmental disorders, respiratory issues, learning difficulties, and behavioural problems.

The Preterm Birth and Healthy Outcomes team focuses on preterm birth in three areas: prediction of who is at risk for preterm birth; prevention of preterm birth; and interventions to improve outcomes for preterm babies. The team is composed of 20 researchers from 13 disciplines, and is led by Dr. David Olson from the University of Alberta and Dr. Suzanne Tough from the University of Calgary.

"We hypothesize that preterm birth is a complex interplay between environment, genetic disposition, fetal factors, and the context within which women live," says Dr. Tough, a Heritage Population Health Investigator. "There's no single factor that would allow us to point to someone and say, 'You're the one who will deliver preterm.' Given all these different types of factors, it makes sense to approach the problem of preterm birth from many angles. That's how we've structured our team."

The team is a collaboration between basic scientists and population researchers: The basic scientists work in areas such as genetics, behavioural neuroscience, and immunology. The population researchers conduct community-based research on the influences of a wide range of socio-economic factors. They will follow one group of 1,000 pregnant women to investigate how they obtain prenatal services; for the major study of prenatal care in Calgary, they will draw their data from another group of 1,200 women. The trial, led by Dr. Tough, will investigate the benefits of delivering prenatal care and education to groups of women at the same stage of pregnancy. Previous work by Dr. Tough has shown that women who are least likely to receive adequate prenatal care are those who are isolated as a consequence of poverty, poor social support, and poor mental health.

"We'll have this amazing database on many, many aspects of women's lives. It will help us understand who is at greater risk for preterm birth," adds Dr. Tough. "The beauty of the team-grant funding is that it will allow for additional data to be collected from the women in this trial, which is supported by the Calgary Health Region."

"We may be able to predict who is at risk for preterm birth"

The potential of the new database has led to some exciting new collaborations. For example, Dr. Inge Christiaens, a Ph.D. student working under the supervision of team co-leader Dr. David Olson at the University of Alberta, has begun to work with Heritage Scholar and team member Dr. Gerlinde Metz from the

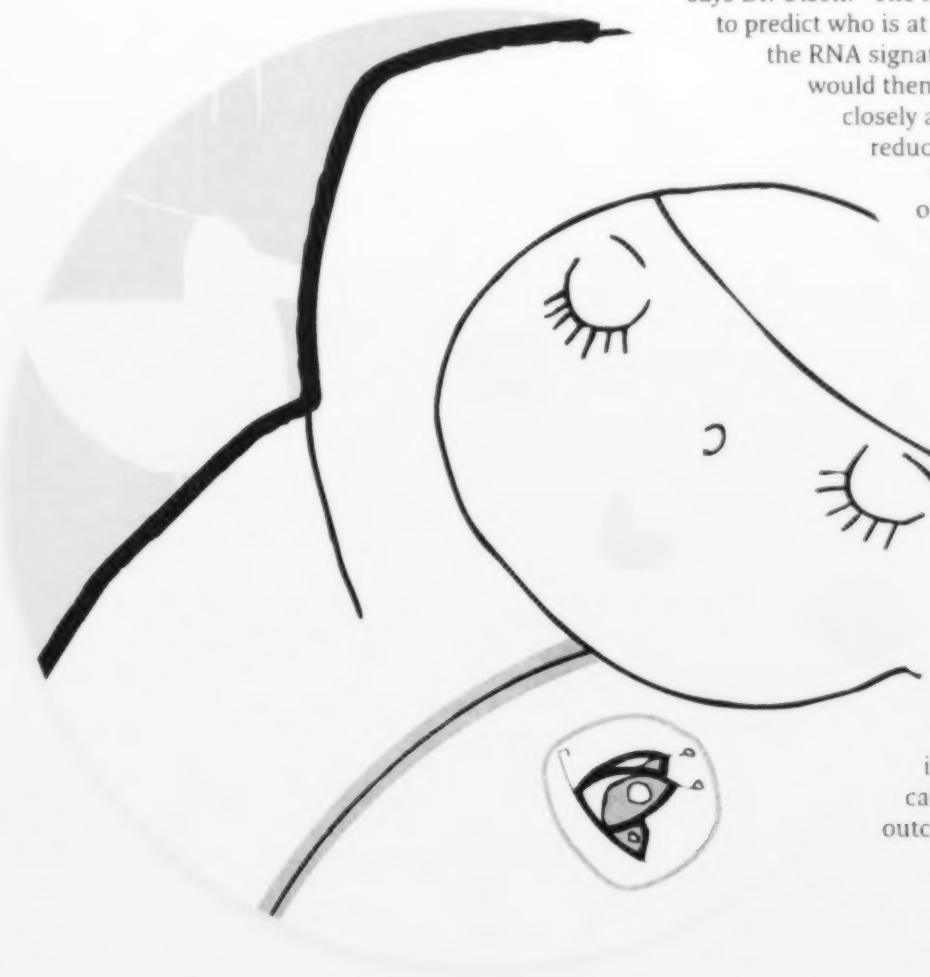
Canadian Centre for Behavioural Neuroscience at the University of Lethbridge. Dr. Christiaens is studying the role stress plays in preterm birth; Dr. Metz has developed an animal model of stress-induced preterm labour. "We're very fortunate to have Dr. Metz join our team, because it adds a new dimension to our research," notes Dr. Olson. "We'll be able to test insights from our work with patients in her model, and vice versa."

Another advantage of the team approach is the way it introduces new expertise into Alberta. The preterm-birth team includes a group of scientists from Toronto and from Perth, Australia, who are specialists in identifying specific patterns of RNA (ribonucleic acid) called RNA signatures. This group has had particular success identifying an RNA signature for women who are in true preterm labour as opposed to threatened preterm labour ("false alarm"), a common cause of hospitalization.

"Our goal is to improve health outcomes for pregnant women"

"We want to see if they can get RNA signatures from non-symptomatic women, whose pregnancies are ticking along just fine," says Dr. Olson. "The idea is that we may be able to predict who is at risk for preterm birth from the RNA signature. If this is possible, we would then watch these women more closely and manage them better to reduce risk.

"Whatever the project, our goal is to improve the health outcomes for pregnant women. I'm confident that at the end of five years, we'll be better able to predict which women are at greater risk for preterm labour. We will have developed more sophisticated interventions to help prevent preterm birth and to sustain pregnancy. And for those children who are born preterm despite our best efforts, we will have interventions that parents can use to ensure better outcomes.

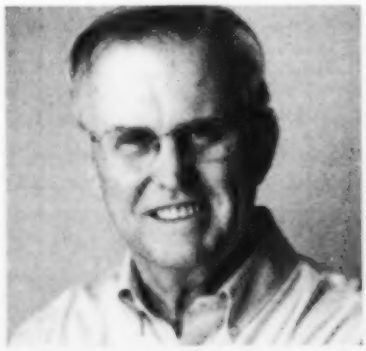


"Beyond what our team will accomplish, we'll have established a legacy in the form of a data repository that will have health records and other linked records on a very large cohort of women and their babies. This will be an enormous research resource for years to come.

"We need people to work in teams to tackle the more complicated questions"

Another key piece of infrastructure that we will set up is a biobank of DNA and reproductive tissue, which will allow [future] researchers to obtain cells and study something that we might not recognize as being of significance today."

And when those researchers look at the data or study the samples, Dr. Tough hopes they will also be working as part of a team. "Science is changing. While there's still a great deal that can be accomplished by individuals working on individual projects, we desperately need people who can work in teams to tackle the more complicated questions. It's not easy; it requires a higher level of collaboration, and you have to learn how to do it. We hope to inspire our next generation of researchers to work in this way, to be able to take the results of research to their community of stakeholders—whether they are other scientists, policy-makers, or health professionals. We want them to make a difference."



Dr. David Olson

Dr. Suzanne Tough

About the team leaders

Dr. David Olson is a professor in the departments of Obstetrics and Gynecology, Physiology, and Pediatrics in the Faculty of Medicine and Dentistry at the University of Alberta. He is the director of the Perinatal Research Centre there.

Dr. Suzanne Tough is an associate professor in the departments of Paediatrics and Community Health Sciences in the Faculty of Medicine at the University of Calgary. She is also the associate director of the Institute of Maternal and Child Health, and the scientific director of the Alberta Centre for Child, Family, and Community Research. She is an *AHFMR Population Health Investigator*.

Selected publications

Olson DM. The promise of prostaglandins: have they fulfilled their potential as therapeutic targets for the delay of preterm birth? *Journal of the Society for Gynecologic Investigation*. 2005 Oct;12(7):466-478.

Tough SC, Johnston DW, Siever JE, Jorgenson G, Slocombe L, Lane C, Clarke M. Does supplementary prenatal nursing and home visitation support improve resource use in a universal health care system? A randomized controlled trial in Canada. *Birth*. 2006 Sep;33(3):183-194.

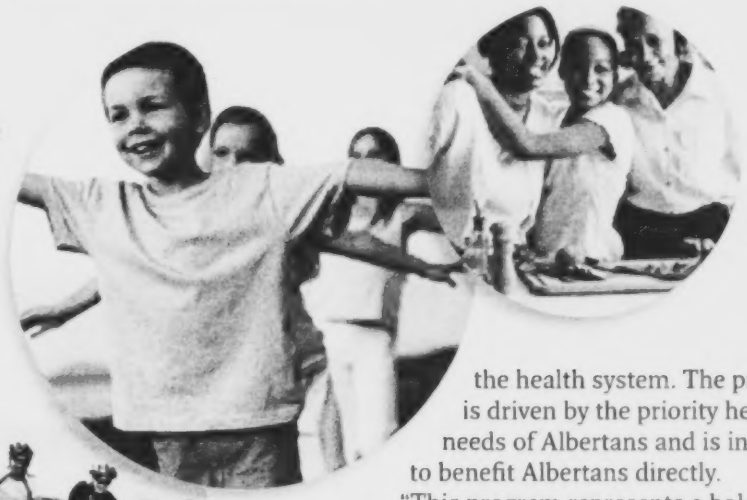
Recommended websites

University of Alberta Perinatal Research Centre
www.ualberta.ca/PERINATAL

Alberta Centre for Child, Family and Community Research
www.research4children.com

A new focus on teams

GREAT ADVANCES IN MEDICAL RESEARCH have come from asking very specific questions: What does a certain gene do? How does one cell recognize another? How does a pathogen get past the body's defences? The answers often provide insights into diseases and form the basis of innovative treatments. AHFMR has a 28-year track record in supporting researchers who ask these questions.



■ But there are broader questions too. Why does Alberta have the highest rate of preterm birth in Canada? How can we prevent osteoarthritis? Answers to these questions could also yield important insights, but they require resources beyond the reach of a single research lab. That's the thinking behind AHFMR's new research-funding initiative: the Interdisciplinary Team Grants program.

This multi-million dollar initiative provides opportunities for collaborative teams of researchers from different disciplines and institutions to address important research questions—questions closely linked with high-priority health problems in Alberta. AHFMR's Interdisciplinary Team Grants program is unique. Though other funding agencies also provide team grants, the AHFMR program boasts a broad, interdisciplinary aspect. It also requires its teams to plan for a way to move their research findings into the health system. The program is driven by the priority health needs of Albertans and is intended to benefit Albertans directly.

"This program represents a bold, new way of supporting research," says AHFMR interim president and CEO Dr. Jacques Magnan. "The varied disciplines of the investigators on these teams will allow them to address issues from all angles—from the basic science behind the problem and the effects across a population, all the way to real solutions to be used in the clinic and policy recommendations to be implemented by decision-makers."

Teams will address high-priority health problems in Alberta

Each AHFMR Interdisciplinary Team Grant is valued at $1 million per year for five years. The program was made possible, in part, by the Alberta government's decision to add $500 million to the AHFMR endowment. That injection of cash allowed AHFMR to increase its basic support for

health research while also initiating pioneering programs such as the Interdisciplinary Team Grants. Alberta Health and Wellness is also contributing more than $15 million over the next five years in support of the program.

For more information on AHFMR's Interdisciplinary Team Grants program and a complete listing of all teams and team members, go to **www.ahfmr.ab.ca** ✲

AHFMR Interdisciplinary Team Grants Recipients 2008

Impact of Maternal Nutrient Status During Pregnancy on Maternal Mental Health and Child Development

Team leaders

Dr. Deborah Dewey
Professor, Paediatrics, Community Health Sciences
Faculty of Medicine, University of Calgary

Dr. Catherine Field
Professor, Nutrition and Metabolism
Faculty of Agriculture, Life and
Environmental Sciences, University of Alberta

Dr. Bonnie Kaplan
Professor, Paediatrics, Community Health Sciences
Faculty of Medicine, University of Calgary

Preterm Birth and Healthy Outcomes

Team leaders

Dr. David Olson
Professor, Obstetrics and Gynecology,
Physiology, Pediatrics
Faculty of Medicine and Dentistry, University of Alberta

Dr. Suzanne Tough*
Associate Professor, Paediatrics,
Community Health Sciences
University of Calgary, Alberta Children's Hospital,
Calgary Health Region

Improving Healthcare Access and Sustainability With Microfluidic Platforms

Team leader

Dr. Linda Pilarski
Professor, Oncology
Faculty of Medicine and Dentistry, University of Alberta

Vaccine Design and Implementation

Team leaders

Dr. Lorne Babiuk
Vice-President (Research), University of Alberta

Dr. James Kellner
Associate professor, Paediatrics,
Microbiology and Infectious Diseases
Faculty of Medicine, University of Calgary

Dr. Anthony Schryvers
Professor, Microbiology and Infectious Diseases,
Biochemistry and Molecular Biology
Faculty of Medicine, University of Calgary

Creating Bone and Joint Health From the Bedside to the Bench and Back Again

Designer Therapies to Reduce the Burden of Osteoarthritis From Mechanisms to Prevention

Team leaders

Dr. Cy Frank**
Professor, Surgery, Kinesiology
Faculty of Medicine, University of Calgary

Dr. Walter Herzog
Professor, Kinesiology, Medicine, Engineering
University of Calgary

Dr. Shoo Lee***
Associate professor, Pediatrics
Faculty of Medicine and Dentistry, University of Alberta

AHFMR awards held:

* Population Health Investigator
** Scientist
*** Health Senior Scholar

Exploring the brain

The co-recipients of the 2008 McLeod Scholarship spend their days delving into the workings of the brain.

Pierre Mattar and Karl Iremonger have a number of things in common. Both are Ph.D. students in the Faculty of Medicine at the University of Calgary. Both are involved in studies of the brain. And now they are co-recipients of a scholarship named in honour of Dr. Lionel McLeod, the first president and CEO of AHFMR.

■ "This award represents security to me," says Mattar, now in the final stages of a six-year doctoral program. "It means I will be supported to finish my Ph.D."

His field is *neurogenesis*, the study of how brain cells are made. His research in the lab of AHFMR Senior Scholar Dr. Carol Schuurmans could lead to ways of replacing brain cells when they become damaged or die. Mattar's work asks some interesting questions: Do genes impact the process of brain-cell development? Does the environment? If so, in what ways?

Understanding how normal brain tissue develops will also lead us to understand processes that could lead to abnormal development. "If you don't know how the car works, it's hard to fix it," he explains. He hopes that his research will one day help others design therapies for those with brain injuries or inherited mental deficiencies.

> Mattar has discovered two genetic pathways

He is making progress. Mattar has discovered two genetic pathways that can be activated in certain cells to make specific types of brain cell—no small feat, considering that there are tens of thousands of types in existence.

Iremonger researches how the activity of these cells gets switched off

Co-winner Karl Iremonger has spent the last two and a half years in the lab of AHFMR Senior Scholar Dr. Jaideep Bains, studying how nerve cells in particular regions of the brain cope with stress and injury. He is especially interested in how these brain cells are affected by physical stressors such as dehydration and severe blood loss. While the objectives of his research can be simply stated, his actual research is far from simple.

Iremonger is studying how the activity of a certain type of brain cell is controlled. When hemorrhage or dehydration occurs, these cells become excited and release a hormone called *vasopressin* into the bloodstream. The correct amount of vasopressin helps the person or animal survive. Too much vasopressin, however, can be a bad thing; excessive quantities contribute to such diseases as congestive heart failure. So Iremonger is also researching how the activity of these cells gets switched off.

Iremonger is not looking for a treatment or cure for one particular disease any more than Mattar is. His work is more general in nature, directed at understanding the basic cellular workings of the brain. The McLeod Scholarship will not only help fund his training and continued research, but will also help motivate him. "Winning this award is a good incentive to keep working hard," says Iremonger. "It's great to be recognized." ❋

About the researchers
Pierre Mattar and **Karl Iremonger** are both Ph.D. students in the Faculty of Medicine at the University of Calgary. They are co-recipients of the Dr. Lionel E. McLeod Health Research Scholarship for 2008.

Selected publication
Mattar P, Langevin LM, Markham K, Klenin N, Shivji S, Zinyk D, Schuurmans C. Basic helix-loop-helix transcription factors cooperate to specify a cortical projection neuron identity. *Molecular and Cellular Biology* 2008 Mar;28(5):1456-1469.

Iremonger KJ, Bains JS. Integration of asynchronously released quanta prolongs the postsynaptic spike window. *Journal of Neuroscience* 2007 Jun 20; 27(25):6684-6691.

Karl Iremonger (left) and Pierre Mattar

AHFMR funding partners

The Alberta Heritage Foundation for Medical Research (AHFMR) has contributed more than $950 million to Alberta's health-research community. The Foundation also relies on the contributions of many partners in building and sustaining health research in this province. To mention just a few, these partners include

- the Government of Alberta and its related ministries and programs;
- federal granting agencies such as the Canadian Institutes of Health Research, the Canada Foundation for Innovation, and the Canadian Health Services Research Foundation;
- international funding partners like the Wellcome Trust and the National Institutes of Health; and
- non-profit and voluntary funding agencies such as NeuroScience Canada, the Heart and Stroke Foundation, the Canadian Diabetes Association, and the National Cancer Institute of Canada.

Following **up**

A former AHFMR researcher follows a different career path

■ Dr. David Matheson sometimes wonders what his life would be like if he had continued along the research path he followed in the early days of his career. For most of the 1980s, he was involved in establishing and supervising his lab at the University of Calgary, which conducted research into immune deficiencies. He was one of AHFMR's first-funded Scholars, and it was an exciting time to be starting out in Alberta.

"The AHFMR grant made a big difference to me. It provided security to my salary, and definitely helped support my lab operations," he says. In 1987, however, Dr. Matheson was recruited to the University of British Columbia to become head of the Division of Immunology at BC Children's Hospital. He went on to become vice-president of medicine there. After almost ten years of dealing with all the complex problems involved in operating any hospital—and the inevitable crises—he asked himself what he really wanted to do and where he would be most effective. In 1998 he left BC Children's to establish his own consulting company in the area of administrative medicine.

Dr. David Matheson

Since then, Dr. Matheson has worked on numerous projects related to the health system. In 2007 he was one of a team of three consultants brought in to conduct a review of the central supply system at St. Joseph's Hospital in Vegreville (east of Edmonton) after unclean surgical tools were discovered. The story dominated news headlines for several weeks. "Our report and recommendations generated a lot of action and a lot of change with respect to infection control and other areas. That is very gratifying to see," he affirms. Two years ago, he was asked to research and develop a strategic plan for the delivery of pediatric care within Ontario's provincial healthcare system. More recently he was called in to conduct a major review of intensive-care systems in Nova Scotia; over the course of a week he visited every ICU in the province.

"I love the flexibility of my work, and the opportunity to work from home after all those years of long hours," he says. Seeing more of his wife is an added advantage.

Though his skills are applied in different ways nowadays, his ultimate goal is the same as it was during his days as a researcher: improving healthcare delivery for everyone's benefit. ❋

About the researcher
Dr. David Matheson received funding as an ***AHFMR Scholar*** from 1981 to 1986 and as a ***Senior Scholar*** in 1986 and 1987, when he also held a ***Major Equipment Grant***.

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